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14. ABSTRACT

As the Alzheimer's disease field moves to studies and intervention trials in the preclinical phase and early prodromal period, it will be necessary to measure everyday function in an increasingly more sensitive and sophisticated way to capture more subtle impairments. One approach to increasing sensitivity in functional measures is to use performance based instruments, such as the UCSD Performance-based Skills Assessment (UPSA), in Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD) research. In this test patients are observed and their response scored as they actually perform proxies for real world tasks and it contrasts with more typical informant based measures. In a preliminary study we compared patients with MCI, patients with mild AD who by diagnosis have functional impairments, and healthy age matched controls on the UPSA, as well as measures of cognition (e.g., episodic memory, semantic memory, executive function, speed). We found that patients with MCI had compromises in everyday functional competence and that the UPSA was strikingly sensitive to these (Goldberg et al, 2010). Additionally the UPSA outperformed an informant based measure on a variety of criteria. *However, that study was not longitudinal.* Therefore, it is important that we obtain data on the longitudinal characteristics of the UPSA in these populations, including the severity of decline in this measure over time, the relationship of decline to cognitive changes in order to determine the validity of the UPSA, and its technical psychometric characteristics (e.g., test-retest reliability)

15. SUBJECT TERMS
Alzheimer's disease, Mild Cognitive Impairment, functional impairment, UPSA

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Abstract

As the Alzheimer's disease field moves to studies and intervention trials in the preclinical phase and early prodromal period, it will be necessary to measure everyday function in an increasingly more sensitive and sophisticated way to capture more subtle impairments. One approach to increasing sensitivity in functional measures is to use performance based instruments, such as the UCSD Performance-based Skills Assessment (UPSA), in Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD) research. In this test patients are observed and their response scored as they actually perform proxies for real world tasks and it contrasts with more typical informant based measures. In a preliminary study we compared patients with MCI, patients with mild AD who by diagnosis have functional impairments, and healthy age matched controls on the UPSA, as well as measures of cognition (e.g., episodic memory, semantic memory, executive function, speed). We found that patients with MCI had compromises in everyday functional competence and that the UPSA was strikingly sensitive to these (Goldberg et al, 2010). Additionally the UPSA outperformed an informant based measure on a variety of criteria. *However, that study was not longitudinal.* Therefore, it is important that we obtain data on the longitudinal characteristics of the UPSA in these populations, including the severity of decline in this measure over time, the relationship of decline to cognitive changes in order to determine the validity of the UPSA, and its technical psychometric characteristics (e.g., test-retest reliability).

In the present longitudinal study we found large between group differences on the UPSA, such that HCs outperformed MCI individuals, who in turn outperformed AD individuals. We did not find a significant effect of time nor a group by time interaction. Psychometrically the UPSA showed very good test-retest reliability. Additionally, correlations between the long form and short form were very high. However, a practice effect was noted at six weeks.

Introduction

As the Alzheimer's disease field moves to studies and intervention trials, it will be necessary to measure everyday function in an increasingly more sensitive and sophisticated way to capture more subtle impairments. One approach to increasing sensitivity in functional measures is to use performance based instruments, such as the UCSD Performance-based Skills Assessment (UPSA), in Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD) research. In this test patients are observed and their response scored as they actually perform proxies for real world tasks (such as determining which bus route to take, writing a check, planning a trip to the beach, and recalling an appointment's time and place). In a preliminary study we compared patients with MCI, patients with mild AD who by diagnosis have functional impairments, and healthy age matched controls on the UPSA, as well as measures of cognition (e.g., episodic memory, semantic memory, executive function, speed). We found that patients with MCI had compromises in everyday functional competence and that the UPSA was strikingly sensitive to these (Goldberg et al, 2010). *However, that study was not longitudinal.* Since our intial review several new measures of everyday function have been introduced. However, these are informant based and may be subject to informant biases, lack of knowledge, or imprecision.

Therefore, it is important that we obtain data on the longitudinal characteristics of the UPSA in these populations, including the severity of decline in this measure over time, the relationship of decline to cognitive changes in order to determine the validity of the UPSA, and its technical psychometric characteristics (e.g., test-retest reliability). We will longitudinally assess magnitude of decline in the UPSA individuals with MCI and

mild AD assessed at baseline, 6 weeks, and 12 months. We will compare and contrast decline in the UPSA with a commonly used measure of function administered to informants (the FAQ) in MCI and AD using Effect Sizes (ES) and mixed model repeated measures. We will determine the cognitive measures that best predict decline in the UPSA. We predict that the UPSA will decline over time in the MCI and AD groups with and demonstrate strong relationships to cognitive decline

Key Research Accomplishments

- Recruitment of subjects for baseline evaluation and longitudinal follow up. To date over 60 subjects have been enrolled and data were analyzed in this report (see below). A total of 147 assessments were completed.
- Implementation of testing procedures and screening procedures. Entry of data into our database.
- We answered key scientific questions listed in our Aims. In particular we found that psychometric properties of the UPSA were robust; that the UPSA was sensitive to diagnostic class such that HCs >MCI>AD in terms of UPSA performance; that in this cohort in which cognitive level was relatively stable over the one year period of follow up, UPSA performance was also stable; and that UPSA short form and long form were highly correlated. We also noted a practice effect for the UPSA at six weeks.

Methods

Subjects

Recruitment began September 21, 2012 with North Shore-LIJ IRB and ORP approval. For the analyses presented here, 36 healthy controls (HCs), 10 individuals with Mild Cognitive Impairment (MCI), and 14 individuals with Alzheimer's disease (AD) were included at baseline. Retention rates for these subjects over the course of this one year longitudinal study (with three assessments) was high at >63%. Nevertheless, as these sample sizes are below are recruiting goals. In order to rectify this we have requested a No Cost Extension (see Appendix).

Demographic data are in Table 1. Mean ages of the groups were in the 72 to 74 year range. Sex ratio was more or less equivalent across groups. The groups were well-educated with approximately 16 years of education.

Results and Discussion

Test retest reliability (over a six week period) was high in the sample at $r>.84$ for both forms ($ps<.0001$).

One of our key analyses consisted of a mixed model repeated measures ANOVA on the UPSA scores. Diagnostic group was a main effect, time (baseline, 6 weeks, one year) was a within subjects effect, and diagnosis*time was the interaction term. Results were as follows (see Tables 3,4).

1. A main effect of diagnostic group was present: HCs>MCI>AD.
2. No effect of time was present.
3. No diagnosis*time interaction was present.

These results suggest two possibilities. First, it is possible that the UPSA, while sensitive to group differences among HC, MCI, and AD groups, may be relatively insensitive to within subject change. The second possibility is that cohort effects were in play, such that groups expected to show decline were instead relatively stable over a 12 month period. We thus explored these possibilities by examining a second measure known to show decline in MCI and AD groups—the Mini Mental State. If this measure did not show change, then we can infer that our UPSA finding was not a measurement characteristic, but rather it was a cohort effect. Indeed, when we subjected our Mini Mental to a mixed model repeated measure, we found large group differences ($p<.0001$), but no time effect ($p>.50$). This result suggests that the MCI and AD groups were rather stable (though it is important to note that both groups declined and declined more than the HC group, albeit non-significantly). It is generally appreciated that many patients with MCI and even AD can display relative cognitive stability for periods of one to two years.

The correlation between the long form and short form of the UPSA was .94 ($p<.0001$). Given the high correlation between the two forms of the test and their high test-retest reliabilities, we suggest that the short form will be utilized more frequently for pragmatic reasons (because it takes less time to administer).

Over six weeks the practice effect in Cohens d effect size units was .33 in the HC group (medium), .56 in the MCI group (medium), and .12 in the AD group (small). These results were somewhat unexpected but others have observed rather large practice effects in MCI and AD samples (Duff et al; Goldberg et al 2015). Over one year the practice effects in Cohens d effect size units were all small (i.e. <0) in the HC group, in the MCI group, and in the AD group.

The results are shown in Figures 1 and 2. A practice effect can be seen at 6 weeks for the HC and MCI groups. Additionally decline from the 6 week timepoint was most evident in the MCI and AD groups.

References

Goldberg TE, Koppel J, Keehlisen L, Christen E, Werringloer U, Conejero-Goldberg C, Gordon ML, Davies P. Performance-based measures of everyday function in Mild Cognitive Impairment. Am J Psychiatry. 2010 Jul;167(7):845-53.

Gomar J, Bobes T, Davies P, Goldberg TE. Development of an UPSA short form for use in Mild Cognitive Impairment and Alzheimer's disease. Am J Geriatric Psychiatry. 2011 Nov;19(11):915-22

Table 1 Group Demographics

Group	Age	Gender	Education	n(baseline)	n(6 week s)	n(1 year)
Healthy Control	71.5 (12.03)	53% male	16.61 (2.57)	36	31	26
Mild Cognitive Impairment	72.8 (10.16)	50% male	17.2 (2.25)	10	9	5
Alzheimer's Disease	74 (10.05)	50% male	15.5 (3.37)	14	8	8

Table 2. Descriptive data for the UPSA long and short forms

Diagnosis=HC

Variable	Mean	Std Dev	Minimum	Maximum	N
MMSE_BL	28.9166667	1.5189282	23.0000000	30.0000000	36
UPSA- _SHORT_1	88.3230453	6.1787890	74.0740741	100.0000000	36
UPSA_ _LONG_1	89.7802095	6.7589245	73.4680135	100.0000000	36
MMSE_6WK	28.3548387	1.7425726	22.0000000	30.0000000	31
UPSA_ _SHORT_2	90.3823178	7.0988087	75.9259259	100.0000000	31
UPSA_ _LONG_2	92.5811882	5.0450183	81.7508418	100.0000000	31
MMSE_1YR	28.6923077	1.5432234	24.0000000	30.0000000	26
UPSA_ _SHORT_3	87.6153846	8.0147195	68.5185185	98.1481481	26
UPSA_ _LONG_3	90.9790210	6.9215856	72.4915825	99.0740741	26

Diagnosis=MCI

Variable	Mean	Std Dev	Minimum	Maximum	N
MMSE_BL	27.0000000	2.3570226	21.0000000	30.0000000	10
UPSA- _SHORT_1	77.0370370	9.1641203	64.8148148	90.7407407	10
UPSA_ _LONG_1	84.2912458	5.7579939	72.8619529	90.8249158	10
MMSE_6WK	26.3333333	2.0615528	24.0000000	29.0000000	9
UPSA_ _SHORT_2	80.8641975	10.7183675	62.9629630	96.2962963	9
UPSA_ _LONG_2	86.5937149	8.7528287	71.9360269	95.8754209	9
MMSE_1YR	26.2000000	1.6431677	25.0000000	28.0000000	5
UPSA_ _SHORT_3	75.1851852	8.7449770	64.8148148	83.3333333	5
UPSA_ _LONG_3	83.9562290	6.1380319	75.5892256	91.6666667	5

Diagnosis=AD

Variable	Mean	Std Dev	Minimum	Maximum	N
MMSE_BL	20.3571429	5.2857885	11.0000000	28.0000000	14
UPSA- _SHORT_1	55.0264550	21.6501455	12.9629630	83.3333333	14
UPSA_ _LONG_1	53.8768639	29.8509381	6.4814815	91.6666667	14
MMSE_6WK	20.5000000	4.7809144	14.0000000	28.0000000	8
UPSA_ _SHORT_2	55.3240741	23.0965032	18.5185185	74.0740741	8
UPSA_ _LONG_2	59.0256734	30.9748460	9.2592593	83.8383838	8
MMSE_1YR	20.2500000	5.7008771	8.0000000	25.0000000	8
UPSA_ _SHORT_3	47.2222222	21.2300557	3.7037037	74.0740741	8
UPSA_ _LONG_3	51.3383838	27.7088757	1.8518519	84.7643098	8

Table 3. Mixed Model Analyses for UPSA Short and Long Forms

Type 3 Tests of Fixed Effects for UPSA Short

Effect	Num DF	Den DF	F Value	Pr > F
Diagnosis	2	138	100.51	<.0001
Time	2	138	1.55	0.2165
Diagnosis*Time	4	138	0.39	0.8186

Type 3 Tests of Fixed Effects for UPSA Long

Effect	Num DF	Den DF	F Value	Pr > F
Diagnosis	2	138	69.37	<.0001
Time	2	138	0.73	0.4816
Diagnosis*Time	4	138	0.15	0.9636

Figure 1. Performance of the three groups over time on the UPSA long form

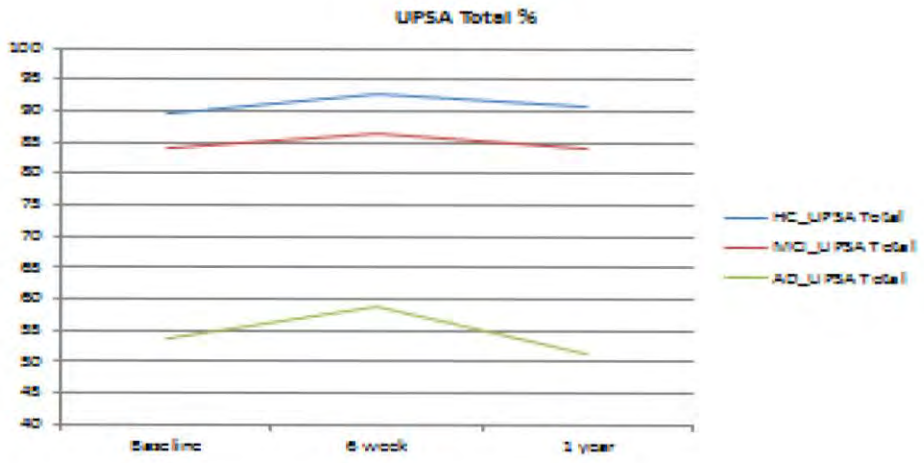
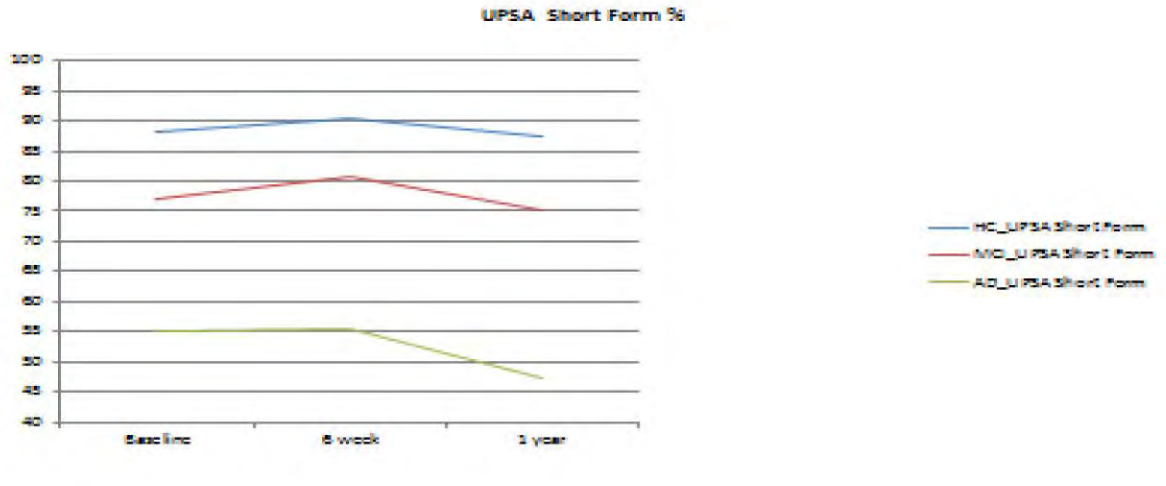


Figure 2. Performance of the three groups over time on the UPSA short form



Appendix I

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March 10, 2015

The Feinstein Institute for Medical Research
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Project Officer, Cheryll Quirin
Telemedicine and Advanced Technology Research Center (TATRC)
US Army Medical Research and Materiel Command (USAMRMC)
Fort Detrick, MD 21702

Dear Ms. Quirin,

I am writing to request a no cost extension (NCE) for a period of 12 months under Award No. W81XWH-12-1-0084 through April 15, 2016 for the project entitled "Longitudinal Study of a Novel, Performance-based Measure of Everyday Functional Competence". The award is currently scheduled to end on April 15, 2015.

The progress on this project was delayed because of slowed recruiting for this ambitious study. While we have recruited nearly 70 subjects with excellent retention across the one year longitudinal study period (incorporating 3 assessments, for a total of nearly 200 assessments) we appreciate the need for more subjects to test our hypotheses fully. We will continue to seek ORP and IRB approval for this ongoing study.

The current award is fully spent, and we will use internal funds to support the study during the extension, including the post-doctoral fellow, study coordinator/recruiter, psychometrician, physician, and Principal Investigator time and effort during this period.

Also enclosed please find an updated SOW and revised timeline. Thank you for your understanding and assistance.

Sincerely,

Rita Nigri
Institutional Official

Terry Goldberg, PhD
Principal Investigator

Enc.
Cc: Dr. Anthony Pacifico